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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 33

Application Number: 08/952,741
Filing Date: November 25, 1997
Appellant(s): Hatada et al.

John W. Bailey
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed May 13, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct but incomplete. The inventions additionally comprises a DNA encoding α-amylase with pH optimum at pH 8-9 that comprises a partial nucleotide sequence of about 20 nucleotides.

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The issues, including changes, are as follows:

1. The rejection under 112, 1st paragraph, (new matter) of claims 3, 4, 15, 16, 20 and 21 is withdrawn by the examiner because the support for the claims can be found in the specification on page 12, lines 1-3, as indicated by Appellants in the Brief (page 10).

2. Whether claims 3, 4, 15, 16 and 20-24 are properly rejected under under 112, 1st paragraph, (written description).

3. Whether claims 3, 4, 15, 16 and 20-24 are properly rejected under under 112, 1st paragraph, (enablement).

4. The rejection under 35 U.S.C. 103(a) of claims 3, 4, 15, 16 and 20-24 as being unpatentable over Ara et al. in view of Tsukamoto et al. or Yuuki et al. is withdrawn by the examiner because of the following. Ara et al. (EP 0670 367 A1, form PTO-1449) teach the enzyme of the instant invention. The rejection of claim 3, with dependent claims 4, 15 and 16, was based on the fact that a DNA encoding a known enzyme is obvious over the enzyme when no sequences are recited. Ara et al. (EP 0670 367 A1, form PTO-1449) teach the enzyme of the instant invention. However, claim 3 is drawn to a DNA encoding alkaline liquefying α-amylase with pH optimum

of 8-9 and having an amino acid sequence wherein one or more amino acids are substituted, deleted or inserted in SEQ ID NO:2, i.e. explicitly not having the amino sequence of SEQ ID NO:2. Therefore, claim 3 does not encompass a DNA encoding SEQ ID NO:2, i.e a DNA encoding a known enzyme. Claim 3 is drawn to a DNA encoding a variant thereof. Said DNA is non-obvious. Claims 22-24 encompass a DNA encoding a variant as well as a DNA encoding SEQ ID NO: 2. However, the claims comprise partial nucleotide sequences that are by themselves unpredictable and, therefore non-obvious.

(7) Grouping of Claims

The appellant provides implicit statement in the brief that claims on appeal should be grouped as follows:

Group I, claims 3, 4, 15, 16 and 20.

Group II, claim 21.

Group III, claims 22-24.

Within each Group all claims stand or fall together with regard to all issues on appeal.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Tsukamoto et al. (1988) Nucleotide Sequence of the Maltohexaose-producing amylase Gene from an Alkalophilic Bacillus sp. #707 and Structural Similarity to Liquefying Type α-amylases. Biochemical and Biophysical Research Communications, vol. 151, pages 25-31.

Yuuki et al. (1985) Complete Nucleotide Sequence of a Gene Coding for Heat- and pH-Stable α-Amylase of Bacillus licheniformis: Comparison of the Amino Acid Sequences of three Bacterial liquefying α-Amylases Deduced from the DNA Sequences. Journal of Biochemistry, vol. 98, pages 1147-1156.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 3, with dependent claims 4, 15, 16 and 20, stands finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 3 is drawn to a DNA encoding an α–amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the specific substrate specificity. There is no limitation on the structural homology with SEQ ID NO:2 or a DNA encoding thereof. Therefore, claim 3 is equivalent to a claim wherein no amino acid sequence is recited. Such variant and a DNA encoding thereof encompass a great number of molecules, both naturally occurring and synthetic, encoding amino acid sequences some of which may not have any structural homology with SEQ ID NO: 2.

Thus, the claims recite an enormous genus of DNAs encoding variant α-amylases from any source characterized only by function and pH optimum.

The specification discloses only a single species of the claimed genus, the DNA encoding a deletion mutant of alkaline liquefying α-amylase having the sequence wherein 32 N-terminal amino acids of SEQ ID NO: 2 have been deleted (specification, paragraph bridging pages 11-12).

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being α-amylase with the specific substrate specificity and pH optimum at pH 8-9 and fails to provide any structure: function correlation present in all members of the claimed genus nor they are

known in the art. Therefore, based on the instant disclosure, it is unpredictable which DNA will encode a mutant alkaline liquefying α-amylase with the desired properties.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

One skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claim 21 stands finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 21 depends from claim 3 and recites additional physico-chemical properties of an enzyme. DNAs encoding said variant amylases encompass a great number of molecules, both naturally occurring and synthetic.

The specification discloses only a single species of the claimed genus, the DNA encoding a deletion mutant of SEQ ID NO: 2, *supra*.

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being α-amylase with the specific substrate specificity and pH optimum at pH 8-9 and fails to provide any

structure: function correlation present in all members of the claimed genus nor they are known in the art.

While the combination of the properties described in claim 21 is imparted by the specific structure and therefore, reflects a certain degree of "structural limitations", those are properties of an enzyme not a DNA. However, an adequate written description of a DNA requires the definition of the specific properties of a DNA itself.

Therefore, based on the instant disclosure, it is unpredictable which DNA will encode a mutant alkaline liquefying α-amylase with the desired properties.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 22-24 stand finally rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 22-24 are drawn to a DNA encoding α–amylase with pH optimum at pH 8-9 from any source comprising a DNA of 20-26 bp not all of which are defined. There is no recitation of any other properties of an enzyme. The DNA of the instant invention

(SEQ ID NO:1) is 1776 bp long. Therefore, at most claims 22-24 recite 1.0-1.5% homology with SEQ ID NO:1. The recited structural feature of the genus (i.e., comprise a fragment of 20-26 nucleotides of SEQ ID NO:1) does not constitute a substantial portion of the genus as the remainder of the structure of a polypeptide with α-amylase activity is completely undefined. Fragments consisting of 20-26 nucleotides of SEQ ID NO:1 are highly unlikely to encode α-amylase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected.

Thus, the claims recite an enormous genus of DNAs encoding α-amylases from any natural source which would include fungi, plants, animals, etc. as well man made amylases characterized only by function and pH optimum.

The specification discloses only two highly homologous species of the claimed genus, the DNAs encoding alkaline liquefying α-amylase of SEQ ID NO: 2 from *Bacillus* sp. KSM-AP1378 (SEQ ID NO:1) and its deletion mutant, *supra*.

The specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of being α-amylase with the specific substrate specificity and pH optimum at pH 8-9 and fails to provide any structure: function correlation present in all members of the claimed genus nor they are known in the art. Therefore, based on the instant disclosure, it is unpredictable which DNA will encode an alkaline liquefying α-amylase with the desired properties.

When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only two species within the genus.

Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 3, 4, 15, 16 and 20-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA encoding an α–amylase having an amino acid sequence of SEQ ID NO:2 and its N-terminal deletion mutant that has a pH-optimum at pH 8-9 and the specific substrate specificity, does not reasonably provide enablement for a DNA encoding an α–amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the requisite properties or for a DNA encoding an α–amylase that has a pH-

optimum at pH 8-9 and comprising a nucleotide fragment of about 20 bp. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the huge number of all possible nucleic acid sequences encoding α–amylases having the specific desired characteristics.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature and breadth of the invention of claims 3, 4, 15, 16, 20 and 21 encompass any nucleic acid sequence encoding any mutant α-amylase having an amino acid sequence of SEQ ID NO:2 with one or more amino acids substituted, added, deleted or inserted and having the specific characteristics from any biological source, or derived by any type of mutation from SEQ ID NO: 2. This reads on any

structure without any structural limitations having an α–amylase activity with the requisite properties.

The nature and breadth of the invention of claims 22-24 encompass any nucleic acid sequence comprising a partial sequence of 20-26 nucleotides of SEQ ID NO:1 and encoding any naturally-occurring or mutant α–amylase having pH optimum at pH 8-9. The specific sequences recited in claims 22-24 represent less than 2% of the entire requisite DNA structure. Thus, with regard to the deficiency of structural limitations claims 22-24 are similar to claim 3. Therefore, one of skill in the art would have been required to make a structure that would impart the requisite properties (claims 3, 4, 15, 16, 20 and 21) or a structure that comprises a specific 20-26 nucleotide fragment and encodes an α-amylase with pH-optimum at pH 8-9 (claims 22-24).

The specification provides guidance and examples for obtaining DNAs encoding an α–amylase having an amino acid sequence of SEQ ID NO:2 from *Bacillus* sp. KSM-AP1378 and its N-terminal deletion mutant. While molecular biological techniques and genetic manipulation to make and use the claimed nucleic acid sequences are known in the prior art and the skill of the artisan are well developed, knowledge regarding the amino acid residues which are important to the enzymatic activity and folding of the α–amylase, the amino acid residues which can be inserted into or deleted from the amino acid sequence of SEQ ID NO: 2 without affecting the requisite specific enzymatic activity, amino acid homology among α–amylases with said specific enzymatic activity

from various biological sources, and the nucleic acid sequence homology among nucleic acid sequences encoding said α–amylases from various biological sources is lacking.

The prior art teaches the DNAs encoding alkaline liquefying α-amylases from *Bacillus* sp. #707 and *Bacillus licheniformis*, respectively (Tsukamoto et al. and Yuuki et al., respectively (form PTO-1449)). The DNAs disclosed by Tsukamoto et al. and Yuuki et al. encode the amino acid sequences which have about 87% and 69% identity to SEQ ID NO:2, respectively. However, the disclosed α–amylases have properties different from the α–amylase of the instant invention. In particular, said α–amylases do not have pH optimum at pH 8-9 (see, for example, Response under 37 CFR 1. 116 filed January 14, 2000, pages 7-8). Therefore, the prior art renders it highly unpredictable as to what amino acid residues can be modified in SEQ ID NO:2 without resulting in drastic changes in the properties of the enzyme.

The specification provides no guidance as to what amino acid residues are responsible for the requisite pH optimum and other specific properties imparted by SEQ ID NO:2 and therefore, what amino acid residues can be mutated without affecting the requisite properties.

Thus, searching for an α–amylase or a mutant thereof with desired characteristics is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a nucleic

acid sequence encoding α–amylase with the requisite characteristics of unknown structure is enormous. Since routine experimentation in the art does not include screening vast numbers of genomic or cDNA libraries constructed from large number of biological sources where the expectation of obtaining the desired α–amylase is unpredictable, one skilled in the art would require additional guidance, such as information regarding the biological source of the enzymes and their enzymatic properties and the amino acids which can be mutated without an adverse effect on the function and properties of the enzyme. Without such a guidance, the experimentation left to those skilled in the art is undue.

(11) Response to Argument

Appellants argue that the rejection of the claims under 35 U.S.C. 112, 1st paragraph (written description) is improper because claim 3 is equivalent of an example in "Revised Interim Written Description Guidelines Training Material" that is directed to "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A-B" (pages 10-11). Appellants argue that the functional limitation "without changing enzymological properties of said amino acid sequence described in SEQ ID NO:2" (emphasis added) in claim 3 is narrower than reference to activity in the Materials' example. This is not agreed with because both, claim 3 and the Example, do not provide the degree of enzymatic activity but imply an

active enzyme. "Without changing enzymological properties" does not mean catalyzing the reaction at a specific rate. However, notwithstanding of that, the rejection is based on the fact that claim 3 describes the enzyme by function and pH optimum only without providing a sufficient structural description. This is because unlimited "more" modifications in "one or more" in claim 3 negates a reference to SEQ ID NO:2. Appellants further argue that "the instant claim 3 does not have a limitation that limits the variants to 95% identity in sequences. However, there are three other elements in claim 3 that definitely describe the genus. The first element is that the generated mutant enzyme must have optimal activity at pH 8-9, the second element is that the enzymological properties are the same as those of an enzyme of SEQ ID NO: 2, and third element is that the mutant enzyme does not cleave pullulan (page 12, 2nd paragraph). This is not persuasive because the second element comprises the first and third elements and said elements are functional. Appellants assert that "the art provides the practitioner with the description of structural constraints similar to what is achieved by the concept of 95% sequence homology" (page 13, 1st paragraph). The examiner disagrees with that because what is present in the Example is not a concept but a limitation which even if the art would provide it, is absent from claim 3. Appellants compare claim 3 with in Fiers and Lilly cases on the basis that "mutant proteins which have amino acids substituted, deleted or inserted [in SEQ ID NO:2] provides structural language" (page 17, 1st paragraph). This is disagreed with for the reasons given

above. Appellants argue that they "have provided how one would screen recombinant microorganisms to identify those expressing an enzyme according to claim 3 (page 19, 1st full paragraph). This is not agreed with as the point of the rejection is the description not the enablement.

Appellants arguments with regard to claim 21 are similar to the presented with regard to claim 3. Claim 21 depends from claim 3 and includes recitations of additional physico-chemical properties. However, there is no additional structural limitation on a DNA compared to claim 3 and there is no recitation of the source of the enzyme. Appellants argue that "this molecular weight range apprises one immediately of the collection of the amino acids that are possible" (page 22, lines 4-5) and further "every possible combination of amino acids that fits in this genus [of amylases with the requisite isolelectric point] is immediately conceivable in this case" (page 22, 1st paragraph). This is not agreed with because not only the isoelectric point is limited but also other diverse properties and one would not be able to visualize the correlation between properties and structures that fit in the genus. Appellants refer to the conserved regions in amylases as structural limitations provided by the art (page 22, 2nd paragraph). It is apparent that these conserved regions are not responsible for the specific properties recited in the claim as changes in the structure as little as about 15% lead to drastic changes in properties, *supra*.

Appellants further argue that claims 22-24 are adequately described because the claims "have both structural and functional language" (page 23). Appellants assert that "there is no ambiguity in this structural element. No variants in this structural element are claimed" (page 24, 1st full paragraph). The recited structural element of the genus encompassed by claims 22-24 does not constitute a substantial portion of the genus as the remainder of the structure of a polypeptide with α-amylase activity is completely undefined. Fragments consisting of 20-26 nucleotide of SEQ ID NO:1 are highly unlikely to encode α-amylase activity and the specification does not define the remaining structural features necessary for members of the genus to be selected.

Appellants argue with regard to the enablement rejection of claims 3, 4, 15, 16, 20 and 21 that "even if the Examiner had met this burden [of presenting the case as to why the claims would not be enabled], Applicants have provided an example that works. Absent some evidence from the Examiner that any mutant enzyme would not work, one must assume that the full scope of the claimed invention is enabled by the specification" (paragraph bridging pages 26-27). As discussed in the rejection above, Appellants enabled SEQ ID NO:1 and its deletion fragment encoding α-amylase activity.

However, the entire scope is not enabled because it is unpredictable from the art and is not taught by the specification as to what changes in the structure are

permissible. Appellants argue that techniques are enabled (page 28). This is correct, but there is no direction provided as to how to use these techniques to make the requisite mutant. Appellants argue that "an important limitation is that the enzymological properties of the enzyme must be the same as those of a protein having the amino acids sequence of SEQ ID NO:2. One of skill in the art can readily determine, by the assay described at page 17, lines 14-22, whether any variant of SEQ ID NO:2 is the same" (paragraph bridging pages 28-29). While one of skill in the art can screen variants and determine their physico-chemical properties, it is unknown from what source to isolate said variants or how to make them by recombinant techniques. Appellants assert that "one of skill in the art would recognize that these [conserved] are not the regions where one would be likely to make additions, substitutions (other than perhaps conservative substitutions) and deletions" (page 29). As discussed above, there is no guidance as to what residues can be modified without affecting the properties.

Appellants argue that "one can not immediately tell from the primary amino acid sequence whether or not a given amino acid sequence for a liquefying α-amylase would be active at the same level as an enzyme having the amino acid sequence of SEQ ID NO:2. Thus, the predictability of function from primary structure is low" (page 30, 2nd full paragraph). The examiner agrees with that. Appellants assert that "the holding in Wands expressly stated that such [screening for activity] was not "undue"

experimentation" (page 30, last paragraph). This is not persuasive because the facts in the instant application and in the Wands case are different. Wands et al. provides the guidance for immunizing the animal with the compound of a known structure (HbsAg) and then further screening cells for negative hybridomas. As it is noted in In re Wands "Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody" (page 1406). The direction of how to make the desired antibody starting with the compound described not only by function but also by structure is, thus, provided in In re Wands. The number of hybridomas to be screened is expected to be large. In the instant case, there is no guidance provided beyond functionality and the teachings are limited to trial and error experiments that makes the experimentation left to those skilled in the art undue.

Appellants argue with regard to the enablement rejection of claims 22-24 "The Board is reminded that the DNA claimed in claims 22-24 comprises these sequences. One of skill in the art recognizes that it is not likely that a DNA including only these sequences would encode an enzyme possessing α-amylase activity having an optimum level at pH 8-9. Rather, many more amino acid would be needed to complete the enzyme structure" (page 36, 1st full paragraph). The examiner agrees with that and bases the rejection on that. Appellants argue that "the working examples show that the short DNA sequences recited in the claims are used in a PCR reaction upon a template DNA from some bacterium that expresses a relevant enzyme. The product is the DNA

of the invention" (page 36, 2nd full paragraph, emphasis added). It is agreed that short DNA sequences recited in the claims can be used in a PCR reaction. Such use is enabled but not claimed. However, Appellants do not teach "some bacterium that expresses a relevant enzyme" as discussed in the rejection. Obtaining a DNA encoding the requisite enzyme from the source containing it is enabled. However, Appellants do not teach said source rendering the experimentation undue.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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